

**COMMITTEE STAFF REPORT
TO THE CHAIRMAN AND RANKING MEMBER**

**COMMITTEE ON FINANCE
UNITED STATES SENATE**

November 2007

**The Intimidation of Dr. John Buse
and the Diabetes Drug Avandia**

A. Introduction

The United States Senate Committee on Finance (Committee) has jurisdiction over the Medicare and Medicaid programs. Accordingly, it has a responsibility to the more than 80 million Americans who receive health care coverage under those programs to oversee the proper administration of these programs, including the payment for medicines regulated by the Food and Drug Administration (FDA). Given the rise in health care costs and the need to maintain public health and safety, Medicare and Medicaid dollars should be spent on drugs and devices that have been deemed safe and effective for use by the FDA, in accordance with all laws and regulations.

This report summarizes the Committee Staff's findings to date regarding GlaxoSmithKline's (GSK) intimidation of an independent scientist who criticized Avandia, a drug GSK manufactures to control glucose levels in diabetics. This report is based upon an intensive review of documents provided by GSK and others.

In a letter dated May 21, 2007, the Committee asked GSK about allegations that its company executives intimidated a research scientist in 1999. At the time of the alleged intimidation, GlaxoSmithKline was called SmithKline Beecham. In 2000, SmithKline Beecham merged with Glaxo Wellcome to create GlaxoSmithKline. Accordingly, throughout this report, the newly formed company will be referred to as GlaxoSmithKline/GSK.

In response to the Committee's letter dated May 21, 2007, that first raised these concerns about retaliation, GSK quickly issued a press release to repudiate the allegation.¹ Specifically, the *Wall Street Journal* wrote, “[GSK] called the suggestion ‘absolutely false.’”² However, internal company documents seem to contradict that claim and reveal what appears to be an orchestrated plan to stifle the opinion of Dr. John Buse, a professor of medicine at the University of North Carolina who specializes in diabetes.

¹ GlaxoSmithKline press release “GSK response to US Senate Committee on Finance” May 21, 2007.

² *The Wall Street Journal*, “Diabetes Expert Raised Issues of Avandia Heart Risk in 2000,” May 24, 2007.

In particular, GSK's attempt at intimidation appears to have been triggered by speeches that Dr. Buse gave at scientific meetings in 1999. During those meetings, Dr. Buse suggested that, aside from its benefit of controlling glucose levels in diabetics, Avandia may carry cardiovascular risks.

The effect of silencing this criticism is, in our opinion, extremely serious. At a July 30, 2007, safety panel on Avandia, FDA scientists presented an analysis estimating that Avandia caused approximately 83,000 excess heart attacks since coming on the market.³ Had GSK considered Avandia's increased cardiovascular risk more seriously when the issue was first raised in 1999 by Dr. Buse, instead of trying to smother an independent medical opinion, some of these heart attacks may have been avoided.

According to documents provided to the Committee by, among others, GSK, and the University of North Carolina, it is apparent that the original allegations, regarding Dr. Buse and GSK's attempts at silencing him are true; according to relevant emails, GSK executives labeled Dr. Buse a "renegade" and silenced his concerns about Avandia by complaining to his superiors and threatening a lawsuit.

Even more troubling, documents reveal that plans to silence Dr. Buse involved discussions by executives at the highest levels of GSK, including then and current CEO Jean-Pierre Garnier. Also, GSK prepared and required Dr. Buse to sign a letter claiming that he was no longer worried about cardiovascular risks associated with Avandia.

After Dr. Buse signed the letter, GSK officials began referring to it as Dr. Buse's "retraction letter." Documents show that GSK intended to use this "retraction letter" to gain favor with a financial consulting company that was, among other things, evaluating GSK's products for investors. After cutting short Dr. Buse's criticism, GSK executives then sought to bring Dr. Buse back into GSK's favor.

While publicly silent subsequent to signing the "retraction letter," Dr. Buse still remained troubled about Avandia and its possible risks. Years later, he wrote a private email to a colleague detailing the incident with GSK:

[T]he company's leadership contact[ed] my chairman and a short and ugly set of interchanges occurred over a period of about a week ending in my having to sign some legal document in which I agreed not to discuss this issue further in public.

Dr. Buse ended the email, "I was certainly intimidated by them.... It makes me embarrassed to have caved in several years ago."

GSK's behavior since the Committee first brought these allegations to light has been less than stellar. Instead of acknowledging the misdeed to investors, apologizing to patients, and pledging to change corporate behavior, GSK launched a public relations campaign of

³ FDA, "Assessment of the cardiovascular risks and health benefits of rosiglitazone," presented July 30, 2007. Estimate presented publicly at FDA advisory committee meeting.

denial. Specifically, GSK sent out a press release titled “GSK Response to US Senate Committee on Finance” which stated that the allegations raised by the Committee were “absolutely false.”⁴ Further, CEO Jean-Pierre Garnier denied having any knowledge of the alleged intimidation of Dr. Buse in an interview that ran in July in *The Philadelphia Enquirer*.⁵

B. Detailed Review of Documents

The Committee initiated an investigation into the risks and benefits associated with the diabetes drug Avandia in the spring of 2007. That investigation was prompted when the *New England Journal of Medicine* published an article by Dr. Steven Nissen and Ms. Kathy Wolski, noting that Avandia was associated with serious cardiovascular risk, including heart attacks.

Dr. John Buse is an expert in diabetes with extensive research experience in the thiazolidinedione (TZD) class of drugs. This class includes Rezulin (troglitazone), Actos (pioglitazone), and Avandia (rosiglitazone). In 1999, Dr. Buse sent a letter to the FDA stating that Rezulin should not be withdrawn over worries about liver toxicity. He noted that the liver toxicity and other safety issues surrounding the alternatives—rosiglitazone and pioglitazone—were not yet known. He noted that the three compounds “are dramatically different in their interaction with their proposed receptor.”

Dr. Buse added that he was a consultant for Takeda-Lilly, the manufacturer of Actos and had been a consultant for SmithKline Beecham, which manufactured Avandia.⁶ Documents from this period show that Dr. Buse was an investigator for a SmithKline Beecham study on rosiglitazone as a treatment for diabetes.⁷

Also in early 1999, Dr. Buse gave speeches at meetings of the Endocrine Society and the American Diabetes Association (ADA). At both meetings, he suggested that Avandia may carry increased cardiovascular risks.

In June 1999, GSK executives discussed Dr. Buse in a series of emails they titled, “Avandia Renegade.” One email reads:

[M]ention was made of John Buse from UNC who apparently has repeatedly and intentionally misrepresented Avandia data from the speaker’s dais in various fora, most recent among which was the ADA. The sentiment of the SB group was to write him a firm letter that would warn him about doing this again...with the punishment being that we will complain up his academic line and to the CME granting bodies that

⁴ GlaxoSmithKline press release “GSK Response to US Senate Committee on Finance,” dated May 21, 2007.

⁵ *The Philadelphia Enquirer*, “Top officer reviews progress at GSK,” July 25, 2007.

⁶ Letter from Dr. John Buse to U.S. FDA, dated February 21, 1999.

⁷ Protocol for 26-week randomized, double-blind study, dated March 3, 1999, and signed by Dr. John Buse.

accredit his activities....The question comes up as to whether you think this is a sensible strategy in the future (we don't really do too much work at UNC to make any threats)

The email series also includes threats that might be made, including a lawsuit and contacting Dr. Buse's colleagues at UNC.⁸ SB in this email refers to SmithKline Beecham which is now GSK.

In response to this series of emails, Dr. Tachi Yamada, GSK's head of research at the time, wrote in an email that he had discussed Dr. Buse with GSK's CEO Dr. Jean-Pierre Garnier as well as David Stout, a senior GSK executive. Dr. Garnier and Mr. Stout are copied on the email. Specifically, Dr. Yamada's email reads:

In any case, I plan to speak to Fred Sparling, his former chairman as soon as possible. I think there are two courses of action. One is to sue him for knowingly defaming our product even after we have set him straight as to the facts—the other is to launch a well planned offensive on behalf of Avandia....

Indeed, Dr. Yamada called Fred Sparling, Dr. Buse's department chairman. Three days later, Dr. Buse wrote a letter to Dr. Yamada attempting to clarify his position on Avandia.⁹ Dr. Buse's letter began, "I wanted to set the record straight regarding all the phone calls and questions I have received...." The phone calls that Dr. Buse referred to were made by GSK officials including Dr. Yamada regarding the speeches that Dr. Buse gave at conferences suggesting cardiovascular problems associated with Avandia.

Dr. Buse continued, "I believe as a clinical scientist that the null hypothesis should be that rosiglitazone has the potential to increase cardiovascular events." Dr. Buse went on to say that his chairman had informed him that GSK executives perceived him as "being for sale" because he received speaking fees from Takeda. Dr. Buse added that he heard "implied threats of lawsuits from my chairman and James Huang...." who was then a product manager with GSK.

Dr. Buse ended the letter to Dr. Yamada by writing, "Please call off the dogs. I cannot remain civilized much longer under this kind of heat."

Along with his letter to Dr. Yamada, Dr. Buse enclosed a separate letter. GSK officials later referred to that second letter as the "Buse retraction letter." In the "retraction letter," Dr. Buse attempted to clarify the remarks he made at the medical conferences regarding Avandia.

On July 1, 1999, Dr. Yamada wrote to Dr. Buse, thanking him for the detailed explanation. Dr. Yamada's email reads, "As you may be aware, my phone call to Fred

⁸ Internal GSK email from William D. Claypool, to Dr. Tachi Yamada, dated June 25, 1999.

⁹ Letter from Dr. John Buse to Dr. Tachi Yamada, undated, with separate letter as enclosure.

Sparling was aimed at being educated....” The letter is copied to CEO Jean-Pierre Garnier.¹⁰

That same day, several GSK employees discussed Dr. Buse in an email chain that questioned whether or not Dr. Buse signed the “retraction letter” that was prepared by GSK. The email reads:

[H]ave you heard back from Dr. Buse? Did he sign your proposed letter?
Assuming he does retract, what are we planning to do to let the world
know that Dr. Buse retracted his statements?¹¹

A second GSK employee responded, “John Buse kindly signed the clarification letter on his letterhead without any change.”¹²

Later that day, the first GSK employee wrote, “I’m not certain what damage has now been caused by the Yamada phone call to [Buse’s] seniors....Maybe we can obtain clarification of how such situations with U.S. opinion leaders in [the] future should be handled. Yeesh!”

On July 2, 1999, several GSK officials discussed whether to share with financial analysts, what they term the “Buse retraction letter.” These financial analysts were evaluating GSK’s products for investors.

In an email, a GSK employee wrote discussed talks he had with the financial analysts. Several GSK executives were copied on this email, including CEO Jean-Pierre Garnier, Dr. Tachi Yamada, and Mr. David Stout. The email reads:

I also discussed how Dr. Buse has also confirmed that caution should be used in comparing the efficacy data and [adverse events] data he presented. That these should not be taken out of context and that the study designs, baselines, etc, etc....were different....As a result of our conversation, [FINANCIAL COMPANY NAME REDACTED] will remove the ‘?’ under the cardiovascular events and they are removing the John Buse table on efficacy presented at the ADA meeting.¹³

But even after Dr. Buse signed the retraction letter, GSK executives were torn over whether or not they could trust the former “Avandia Renegade.” On one hand the documents reveal that some GSK executives were eager to work with Dr. Buse. For instance, in late November 1999, a GSK official sent an email to several executives which read, “We need to see John Buse ASAP now that we know that he is involved with the NIH [study].”¹⁴

¹⁰ Letter to Dr. John Buse, dated July 1, 1999.

¹¹ Internal GSK email from Thomas Leonard to Sharon W. Shapowal, dated July 1, 1999.

¹² Internal GSK email from Sharon W. Shapowal to Thomas Leonard, dated July 1, 1999.

¹³ Internal GSK email from Tom Curry, dated July 2, 1999.

¹⁴ Internal GSK email from James Huang, dated November 29, 1999.

On the other hand, others at GSK never fully believed that Dr. Buse had completely dropped his concerns with regard to Avandia and its possible cardiovascular risks. In fact, even though Dr. Buse remained silent in public, he continued privately to voice his opinions about cardiovascular problems with Avandia. For example, after signing the retraction letter, Dr. Buse wrote to the FDA Commissioner in March 2000 where he noted:

In short, the lipid changes with troglitazone and pioglitazone can only be viewed as positive. They are very similar in nature....As mentioned above, I remain concerned about the lipid changes with rosiglitazone....Rosiglitazone is clearly a very different actor. I do not believe that rosiglitazone will be proven safer than troglitazone in clinical use under current labeling of the two products. In fact, rosiglitazone may be associated with less beneficial cardiac effects or even adverse cardiac outcomes.

The following month, GSK officials acquired a copy of Dr. Buse's letter to the FDA. GSK executives faxed Dr. Buse's FDA letter among themselves with a cover note reading, "We need to address this as a company....Looks like Dr. Buse doesn't buy into our lipid or cardiovascular story."¹⁵

Following Dr. Buse's FDA letter, GSK drafted another letter to Dr. Buse from one of its executives, Martin Freed. The letter reads, "I remain concerned about your ongoing aggressive posture towards rosiglitazone and SmithKline Beecham. In my opinion, you have presented to [FDA] several unfair, unbalanced, and unsubstantiated allegations."¹⁶

Later in 2000, Dr. Buse reached out to GSK officials, asking them to sponsor a continuing medical education (CME) program about TZD use. Dr. Buse wrote in his request:

I spoke to Rich Daly, the head of marketing (and sales?) for Takeda. He was going to run the idea of joint support for the CME program by the Takeda lawyers to make sure there are no FTC issues in what I proposed. I highlighted to him that the benefit to Takeda and [SmithKline Beecham] would be the potential to grow interest in the class as a whole and as a very public display of the end of the "glitazone wars."¹⁷

By late 2000, GSK officials appeared to believe that they had the former "Avandia Renegade" under control. Emails from this time refer to GSK as "SB," as GSK had not yet been created from the merger. In November, a GSK/SB executive wrote:

¹⁵ Fax from Eric Kimbro to Brian Blakey, dated April 19, 2000.

¹⁶ Draft letter to Dr. John Buse from Martin I. Freed, undated.

¹⁷ Email from Dr. John Buse to Daniel Tasse, dated June 23, 2000.

Just a quick note about your comment on Buse....I am getting messages that he is really coming around to the SB side of things. He has stopped his out-right bashing and is now more TZD positive with kind comments on Avandia.....David Pernock spoke to him and said something to the effect that [Glaxo Wellcome] is his friend now but GSK will be the future and he needs to realize that....

I spoke to him separately on a couple of occasions...and let him know that our relationship got off on the wrong foot but that is in the past and we want to move on from here.... FYI and thanks for your help in bringing J. Buse back to the middle and hopefully beyond.¹⁸

However, based upon the documents in the Committee's possession, GSK executives continued to try and shape Dr. Buse's views regarding Avandia. For example, in early 2001, Dr. Buse contacted GSK officials, requesting citations for a textbook he was writing. One official suggested that GSK should both provide and interpret the information for Dr. Buse, stating in an email:

Our chances on having Buse reflect our views and messages will be enhanced greatly if we tell him what they are rather than relying on him to development [sic] on his own accord via examining data.... [F]inally our view of the big picture lipid story including LDL characteristics and fat redistribution cannot be easily gleaned from our collection of pieces. There is no evidence that Dr. Buse will come to these views without some guidance and support. Of course care will need to be taken to work any overview pieces in a way that appears academic rather than too commercial to enhance the probability that Dr. Buse will adopt our views as his own.¹⁹

Concern with Dr. Buse reemerged in 2002, as his professional stature grew. That September, GSK officials discussed bringing him further into the fold. A GSK official described him as the "most powerful Endocrinologist in the Carolinas.... [H]e is gaining power nationally and internationally." The email continued:

[We feel] as if Dr. Buse [is] primed to move to a more middle-of-the-road stance concerning TZDs. The timing for this 'shift' has to be right. In my opinion, that right time will be with the launch of Avandamet. He is very excited about the launch of this new combo product and very critical of [COMPANY NAME REDACTED] for not moving faster on their combo....His experience with and advocacy for Avandamet could prove invaluable for it's [sic] in the Blue Ridge region and beyond.²⁰

¹⁸ Internal GSK email from Michael DiMatteo to Martin I. Freed, dated November 3, 2000.

¹⁹ Internal GSK email from Thomas B. Leonard to Michael DiMatteo, dated January 12, 2001.

²⁰ Internal GSK email from Harry G. Roberts to Michael DiMatteo, dated September 3, 2002.

A different GSK official responded, “As long as we are on the same page, we could consider him....”²¹ The following week, another official wrote, “It looks like marketing would like us to move forward using Dr. Buse as an investigator in the Avandamet program. Are you OK with this?”²² Avandamet refers to a combination drug for glucose control that combines Avandia with metformin.

Based on the documents in the Committee’s possession, it appears that Dr. Buse remained silent about his concerns regarding Avandia for approximately two years. However, in 2005, he once again privately voiced his opinion that Avandia carried cardiovascular risks. In an email he sent to Dr. Steven Nissen, chairman of the Cardiology Department at the Cleveland Clinic, he again revealed his ongoing concerns about Avandia and described his treatment by GSK. Specifically, Dr. Buse wrote:

Steve: Wow! Great job on the muriglitazar article. I did a similar analysis of the data at rosiglitazone’s initial FDA approval based on the slides that were presented at the FDA hearings and found a similar association of increased severe CVD events. I presented it at the Endocrine Society and ADA meetings that summer. Immediately the company’s leadership contact[ed] my chairman and a short and ugly set of interchanges occurred over a period of about a week ending in my having to sign some legal document in which I agreed not to discuss this issue further in public.

Later in the email, Dr. Buse confirmed GSK’s treatment of him when he wrote, “I was certainly intimidated by them but frankly did not have the granularity of data that you had and decided that it was not worth it.”

Dr. Buse concluded in his email, “Again congratulations on that very important piece of work. It makes me embarrassed to have caved in several years ago.”²³

C. Conclusions

The documents in the Committee’s possession raise serious concerns about the culture of leadership at GSK. Even more serious perhaps is our fear that the situation with Dr. Buse is part of a more troubling pattern of behavior by pharmaceutical executives.

Specifically, in 2004, Dr. Gurkirpal Singh of Stanford University testified at a Committee hearing that an executive at Merck sought to intimidate him by calling his superiors. Merck also warned Dr. Singh that they would make life very difficult for him, if he persisted in his request for data on Merck’s drug, Vioxx. It was later discovered that Vioxx increased the risk of heart attacks and it was withdrawn from the market.²⁴

²¹ Internal GSK email from Alexander R. Cobitz to Michelle L. Chung, dated October 10, 2002.

²² Internal GSK email from Susan Weill to Sharon W. Shapowal, dated October 21, 2002.

²³ Email from Dr. John Buse to Dr. Steven Nissen, dated October 23, 2005.

²⁴ <http://www.senate.gov/~finance/hearings/testimony/2004test/111804GStest.pdf>

Merck's intimidation of Dr. Singh as it sought to protect Vioxx bears striking similarities to apparent threats by GSK against Dr. Buse to protect Avandia. The Committee is very concerned that this behavior may be more prevalent in the pharmaceutical industry than is evidenced by these two cases.

Corporate intimidation, the silencing of scientific dissent, and the suppression of scientific views threaten both the public well-being and the financial health of the federal government, which pays for health care. The behavior of GSK during the time that Dr. Buse voiced concerns regarding the cardiovascular risks he believed were associated with Avandia was less than stellar. Had Dr. Buse been able to continue voicing his concerns, without being characterized as a "renegade" and without the need to sign a "retraction letter," it appears that the public good would have been better served.

D. Terms

American Diabetes Association or ADA – an American health organization providing diabetes research, information and advocacy.

Avandamet – a GlaxoSmithKline drug to treat diabetes that combines Avandia (rosiglitazone) and metformin.

Avandia (rosiglitazone maleate) – brand name of oral diabetes drug which controls glucose in diabetics. The generic name is rosiglitazone maleate. GlaxoSmithKline manufactures Avandia.

Buse, John – a professor of medicine at the University of North Carolina.

Cardiovascular disease or CVD – refers to the class of diseases that involve the heart or blood vessels (arteries and veins).

Federal Trade Commission or FTC – an independent agency of the United States government which promotes consumer protection and eliminates and prevents anticompetitive business practices.

Food and Drug Administration or FDA – an agency of the United States Department of Health and Human Services, which is responsible for regulating the safety of food and drugs.

Garnier, Jean-Pierre – CEO of SmithKline Beecham (SB) which later became GlaxoSmithKline (GSK).

GlaxoSmithKline or GSK – the company formed in 2000 by the merger between Glaxo Wellcome and SmithKline Beecham.

Lipids – broadly defined as any fat-soluble (lipophilic), naturally-occurring molecules. Generally, LDL transports cholesterol and triglycerides from the liver to peripheral tissues.

Low-density lipoprotein or LDL – a lipid that is associated with heart disease. Sometimes called “bad” cholesterol.

National Institutes of Health or NIH – the primary agency of the United States government responsible for biomedical research.

Nissen, Steven – chairman of the Cardiology Department at the Cleveland Clinic.

Pioglitazone – diabetes drug which controls glucose in diabetics. Takeda-Lilly markets pioglitazone as Actos.

Rosiglitazone – diabetes drug which controls glucose in diabetics. GlaxoSmithKline sells a branded version called Avandia.

SmithKline Beecham or SB – see definition for GlaxoSmithKline.

Sparling, Fred – Chair of the department of medicine at the University of North Carolina.

Stout, David – a senior executive at GlaxoSmithKline.

Thiazolidinedione or TZD – drug class used for therapy in type 2 diabetes. Members of this class include Rosiglitazone (Avandia), Pioglitazone (Actos), and Troglitazone (Rezulin), which was withdrawn from the market due to an increased incidence of drug-induced hepatitis.

Troglitazone (Rezulin, Resulin, or Romozin) – drug in the thiazolidinedione class. It was introduced in the late 1990s but turned out to be associated with liver toxicity. It was withdrawn from the U.S. market on March 21, 2000, and from other markets soon afterwards.

Yamada, Tachi – formerly GlaxoSmithKline's head of research and development.

E. Timeline

Early 1999 – Dr. John Buse gives several talks that are critical of Avandia.

June 25, 1999 – GSK executives discuss Dr. Buse as the “Avandia Renegade.” Dr. Tachi Yamada then calls Dr. Buse’s department chairman at the University of North Carolina to complain.

Interim time period – Dr. Buse sends a letter to Dr. Yamada asking him to “call off the dogs.” He attaches a separate letter, later referred to by GSK as the “Buse retraction letter.”

July 2, 1999 – GSK executives discuss the “Buse retraction letter” and consider sending it to financial consultants who are evaluating GSK’s products for investors.

March 2000 – Dr. Buse sends a letter to the FDA Commissioner. He writes that he is concerned that Avandia “may be associated with less beneficial cardiac effects or even adverse cardiac outcomes.”

April 19, 2000 – GSK acquires a copy of Dr. Buse’s letter to the FDA. A GSK executive writes, “We need to address this as a company....Looks like Dr. Buse doesn’t buy into our lipid or cardiovascular story.”

November 3, 2000 – GSK officials discuss Dr. John Buse internally. One GSK executive writes to another, “[T]hanks for your help in bring J. Buse back to the middle and hopefully beyond.”

October 2005 – Dr. Buse writes a private email to a fellow research scientist and complains that he was intimidated by GSK back in 1999. Dr. Buse writes, “I was certainly intimidated by them....It makes me embarrassed to have caved in years ago.”

May 21, 2007 – Senate Finance Committee asks GSK about allegations that the company intimidated a scientist for raising concerns about the cardiovascular risks of Avandia. GSK responds with a press release to counter the allegations.

May 24, 2007 - Reporting on the allegations of intimidation, *The Wall Street Journal* writes, “[GSK] called the suggestion ‘absolutely false.’”²⁵

²⁵ *The Wall Street Journal*, “Diabetes Expert Raised Issues of Avandia Heart Risk in 2000,” May 24, 2007.